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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,544	04/27/2001	Defu Zeng	STAN 190	3043

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EXAMINER	
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Commissioner for Patents

The Examiner's response to new issues raised in Appellant's Reply Brief filed 6/8/05 is attached.

1. The reply brief filed 6/8/05 has been entered and considered. The application has been forwarded to the Board of Patent Appeals and Interferences for decision on the appeal.

2. Responsive to Appellants Reply Brief filed on 6/8/05, a supplemental Examiner's Answer is set forth below:

The new issues raised by Appellants in the said reply brief and the Examiner's arguments are as follows.

- Referring to the paragraph spanning pages 3 and 4 of Appellants said Reply Brief, Appellants argue that Amano *et al* teach that the antibody 3C11, which blocks the proliferation of CD1-restricted T cells in response to CD1-transfected B cells, failed to demonstrate a significant expression of CD1 on B cells from wild type mice:

It is the Examiner's position as to the teaching Amano *et al* that Applicant argues is as follows: "The failure of 3C11 to demonstrate a significant expression of CD1 on B cells from wt [wild-type] or β2m -/- mice as assessed by FACS could suggest that the β2m-independent form [of CD1] is expressed below the threshold level of detection on most B cells, or that only a small subset (<1%) of B cells in the spleen expresses this form."

The Examiner notes that Amano *et al* continue on "It is of note that 3% of splenic B cells in β2m -/- mice showed dull staining for CD1 when a bright counterstain was used in conjunction with 3C11 mab...". Thus, Amano *et al* recognized that there was a difference between the sensitivity required for inhibition of proliferation *vs* staining using 3C11, and that it was possible that only a small subset of B cells in the spleen expresses the β2m-independent form of CD1.

It is the Examiner's further position that Amano *et al* teach that staining of normal splenic B cells with mAb 3C11 (that recognizes both β2m and β2m-independent forms of CD1) identified a distinct population accounting for about 15% of B cells that stained brightly for CD1 (page 1715 at the first sentence of the third paragraph at column 1, second paragraph at column 2 on page 1711). In addition, Amano *et al* teach that 3C11 inhibited the proliferation of CD1-restricted T cell clones in response to LPS-activated wild type spleen cells, and that these B cells expressed CD1 (fourth and fifth full paragraphs at column 2 on page 1714), and that in β2m-/- mice, about 50% of marginal zone splenic B cells expressed CD1 (first full paragraph at column 2 on page 1715). It is the Examiner's position that the presence of CD1 was demonstrated on splenic B cells, and the finding of CD1 expression using the methodology taught by Amano *et al* on 1% to 15% of cells is not a teaching away (the Examiner assumes that Appellants direct their argument to this point with regard to CD1 expression on B cells).

- It is Appellant's position that the summary of the reference Amano et al fails to consider the unusual model system upon which the reference is based (page 3 at lines 1-2 of Appellant's Reply Brief):

It is the Examiner's position as to Appellant's argument that the summary of the reference fails to consider the "unusual model system" upon which the reference was based (referred to by Appellants in the Appeal Brief on page 6 at line 3 as "artificial features of this model system"), the Examiner has addressed these issues in the "(10) Response to Argument" section of the Examiner's Answer mailed 5/9/05.

- It is Appellant's position (on page 5 at the second full paragraph), as to the teaching of Amano *et al* (at page 1716, column 2, second paragraph) that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZB mice is mediated by the $CD1^{hi}$ subset of B cells is in reference to experiments that were conducted by Zeng *et al* in a manuscript that was not published prior to the filing of the priority document to the present application, that one cannot determine based on this sentence if the spontaneously secreted antibodies relate to disease, if the cells were actually involved in the disease process, if the spontaneous secretion was *in vivo*, whether CD1 played a causative role in the secretion of antibody, or whether blocking CD1 would have an effect on the antibody secretion:

It is the Examiner's position that Amano *et al* teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZB mice is mediated by the $CD1^{hi}$ subset of B cells, and that the remainder of Appellant's objections are being argued separately. As has been enunciated in the rejections of record, Zeng *et al* teach that the severity of disease is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a, this secretion of autoantibodies being *in vivo*, that T cells expressing the TCR specific for CD1 were involved in the disease process, and Amano *et al* teach that mutual activation of anti-CD1 T cells and B cells results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG, and that TCR/CD1 interaction can be blocked by administration of anti-CD1 mAb.

- It is Appellant's position (on page 5 at the section "The Examiner's summary of Zeng *et al* ..." and continuing on to page 9) that important information as to the teachings has been omitted:

It is the Examiner's position that Appellant's summary of Examiner's summary of Zeng *et al* is missing important points. It is the Examiner's further position that the teachings of Zeng *et al* are set forth in full in the rejections of record in the Examiner's Answer mailed 5/9/05 on page 5 at lines 18-22, pages 6-7, page 10 at lines 11-24, and page 11 at lines 1-12.

- With regard to Appellant's point 1 on page 6, Appellants go into more detail to argue an issue that has already been argued:

It is the Examiner's position that the art teachings are also pertinent with respect to Appellant's more detailed comments pertaining to this issue, and as enunciated by the Examiner on page 15 of the Examiner's Answer mailed 5/9/05 at lines 16-22 at "(2)", *i.e.*, as to the athymic and lethally irradiated hosts, the Examiner repeats that irradiation and lack of thymus serves to eliminate endogenous competing cells; Zeng *et al* recognize that their transgenic mice (or euthymic hosts) developed symptoms of SLE, but did not develop overt SLE due to the contribution of endogenous non-transgenic T cells that effectively competed with the transgenic T cells (the antigen-induced expression of transgenic cells is markedly inhibited by the presence of the thymus in the adoptive hosts, thus necessitating transfer of the transgenic T cells in to nude mice). The Examiner reminds Appellants that Zeng *et al* and Amano *et al* correlate their teachings using experimental models with teachings that use the same experimental model as Appellant's, as well as with teachings relating to hereditary murine SLE and to other models of hereditary murine SLE, for example, the MLR/lpr mouse model.

- With regard to Appellant's comments (on page 7 at the third full paragraph) that the teaching of the critical role the cytokine secretion patterns of T cells plays in regulating B cell activation does not bear on the role of CD1 in spontaneous lupus because Appellants are not claiming the manipulation of cytokine secretion profiles for the treatment of lupus:

It is the Examiner's position that the important teaching is not manipulation of cytokine secretion profiles as such for the treatment of lupus, but rather the correlation of cytokine secretion profiles of T cells that recognize CD1 in hereditary lupus with whether or not they are protective or inductive of disease because the cytokine secretion pattern of T cells plays a critical role in regulating B cell activation, the cells that produce the autoantibodies.

- With regard to Appellant's comments (on page 7 of the Reply Brief at the last paragraph and continuing on to page 8 at the first paragraph pertaining to Zeng *et al*), that there is a teaching away from the claimed invention because depletion of T cells that recognize CD1 exacerbates the development of lupus, Appellants argue that the depletion of T cells that recognize CD1 exacerbates development of lupus, and that this trait of CD1 recognition is shared by the $CD4^{-}CD8^{-}$ T cell subset in the marrow that prevented lupus:

It is the Examiner's position that the teaching is not a teaching away because the depletion is of one T cell subset, $NK1.1^+$ Vα14 cells that secrete the disease-protective cytokine IL-4, and this depletion occurs just prior to disease development. In addition, Applicant is arguing this point separately because Amano *et al* teach that the $NK1.1^+$ T cells with the Vα14 TCR recognize β2m dependent form of CD1 on syngeneic B cells, but that non-Vα14 TCRs recognize both the β2m-dependent and independent forms of CD1 on syngeneic B cells, indicating that there is more than one subset of T cells that recognize CD1 and more than one form of CD1 (Amano *et al*, page 1710, column 2 at the second full paragraph). The teaching of exacerbation of lupus by eliminating a subset of T cells that produces high levels of IL-4 and recognizes CD1 indicates that these cells are protective, and this is consistent with the teaching of a marrow $CD4^-CD8^-$ subset of T cells that produce high levels of IL-4 and recognize CD1, this subset also being protective.

In addition, Appellants state at lines 1-2 on page 2 of the reply brief that "there is no reasonable expectation that interfering with CD1 would be beneficial, rather than deleterious to the development of disease;" however, Appellants do not provide arguments or point to teachings in the art to support their position, making the said argument spurious.

Appellant may file another reply brief in compliance with 37 CFR 41.41 within two months of the date of mailing of this supplemental Examiner's Answer. Extensions of time under 37 CFR 1.136(a) are not applicable to this two month time period. See 37 CFR 41.43(b)-(c).

A Technology Center Director or designee has approved this supplemental Examiner's Answer by signing below:

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January 9, 2006

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